Public Citizen

Buyers Up • Congress Watch • Critical Mass • Global Trade Watch • Health Research Group • Litigation Group
Joan Claybrook, President

May 4, 1999

Jane Henney, M.D.
Commissioner,
Food and Drug Administration
Rockville, MD 20857

CITIZEN'S PETITION TO REVISE THE LABELING ON TAMOXIFEN (NOLVADEX)

Public Citizen, with a membership of more than 150,000, and the National Women's Health Network, with a membership of more than 12,000, both nationwide consumer organizations, hereby petition the Food and Drug Administration (FDA), pursuant to the Federal Food, Drug and Cosmetic Act 21 U.S.C. Section 355(e)(3), and 21 C.F.R. 10.30 to urge that the FDA require a Medication Guide for patients and revise the physician prescribing information for tamoxifen (Nolvadex). Attached to this petition is our suggested Medication Guide when tamoxifen is prescribed to reduce the incidence of breast cancer in women at high risk of the disease.

When tamoxifen, a known human carcinogen, is prescribed to healthy women, there must be compelling evidence of great benefit. Although we are not convinced that the benefits of tamoxifen outweigh its risks in this population, tamoxifen has been approved and is now being prescribed for the reduction in incidence of breast cancer. As long as this use occurs, it is imperative that the data be clearly presented and the risks and benefits clearly stated. We feel that the current FDA-approved label for reduction in breast cancer incidence provides inadequate information and is difficult to interpret for both patients and physicians.

ACTIONS REQUESTED AND BASIS OF PETITION:

We recommend the following changes:

PATIENT MEDICATION GUIDE

- *Separate the two major indications* (**breast cancer treatment** and **reduction in incidence of breast cancer**) into *two separate guides* which would include Clinical

Ralph Nader, Founder
1600 20th Street NW • Washington, DC 20009-1001 • (202) 588-1000

Studies, Indications and Usage, Contraindications, Precautions, and Adverse Reactions. Two separate Medication Guides would prevent the confusion now present where readers find it difficult to discern what is relevant to their particular indication.

- For each indication, clear risk/benefit information is needed.
- Add a clear statement as to what tamoxifen does and does not do.
- Revise the description of the Royal Marsden Study[1] for reduction in incidence in breast cancer. The Royal Marsden Study, though different in some respects from the trial that was the basis for approval of tamoxifen (the P-1 Trial[2]) had the power to detect a tamoxifen "preventive" effect, had one existed.[3]
- Remove repetitive information. Repetition creates confusion and makes it difficult for the reader to discern what is really important.
- Add information from other tamoxifen studies including possible adverse events not

---

[1]Powles T, Eeles R, Ashley S, et al. Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomized chemoprevention trial. *Lancet* 1998;353: 98-101.

[2] Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the national surgical adjuvant breast and bowel project P-1 study. *Journal of the National Cancer Institute* 1998;90:1371-1388.

[3]Powles T., M.D., Royal Marsden NHS Trust; Transcript of the Oncology Drug Advisory Committee meeting, September 2, 1998, p.128

monitored in the P-1 trial, e.g., ocular toxicity and uterine pathology.[4,5,6,7,8,9] (In the P-1 trial, baseline endometrial sampling was optional for 11,000 out of the approximately 13,000 women enrolled, and eye exams were not required; thus, we do not have reliable incidence data from this study on these adverse effects.)

- Add exclusion criteria that were used in the P-1 trial and that are not in the current label:
  Life expectancy less than 10 years;
  Prior or suspected breast cancer of any type: invasive; ductal carcinoma *in situ* (DCIS) or lobular carcinoma *in situ* (LCIS) treated with mastectomy, radiation, or systemic adjuvant therapy;
  Prior malignancy less than 10 years ago, except carcinoma *in situ* (CIS) of the cervix or basal/squamous cell carcinoma of the skin;
  Existing nonmalignant disease which precludes use of tamoxifen;
  Performance status that restricts normal activity for a significant portion of the day;
  Estrogen or progesterone replacement therapy, oral contraceptives, androgens (unless stopped three months before taking tamoxifen);
  Prior use of tamoxifen;
  Prior history of macular degeneration;
  Concurrent use of chemotherapy;
  Refusal to undergo endometrial sampling or unsuccessful sampling (if the woman has an intact uterus).

- Add a clear statement as to who should and should not take tamoxifen and why.

---

[4]Ah-Song R, Sasco AJ. Tamoxifen and ocular toxicity. *Cancer Detection and Prevention* 1997;21:522-531

[5]Berliere M, Charles A, Galant C, Donnez J. Uterine side effects of tamoxifen: a need for systemic pretreatment screening. *Obstetrics & Gynecology* 1998;91:40-44

[6]Magriples U, Naftolin F, Schwartz PE, et al. High-grade endometrial carcinoma in tamoxifen-treated breast cancer patients. *Journal of Clinical Oncology* 1993;11:485-490

[7]Ross D, Whitehead M. Hormonal manipulation and gynaecological cancer: the tamoxifen dilemma. *Current Opinion in Obstetrics and Gynecology* 1995;7:63-68

[8]Ramondetta L, Sherwood JB, Dunton CJ, et al. Endometrial cancer in polyps associated with tamoxifen use. *American Journal of Obstetrics Gynecology* 1999;180:340-341

[9]Rutqvist LE, Johansson H, Signomklao T, et al. Adjuvant tamoxifen therapy for early stage breast cancer and second primary malignancies. *Journal of the National Cancer Institute* 1995;87:645-651

- Emphasize the increased incidence of serious adverse effects in women over 50.

- Add a contraindication for nursing mothers.

- Add a clarification of the limitations of the model used to predict breast cancer risk (the Gail model).

REVISED PHYSICIAN LABEL

- *Separate the two major indications* (**breast cancer treatment** and **reduction in incidence of breast cancer**) into clearly distinct sections of the label (Clinical Studies, Indications and Usage, Contraindications, Precautions, Adverse Reactions). Two separate sections would prevent the confusion now present where readers find it difficult to discern what is relevant to their patients' particular indication.

- Add clear risk/benefit information for each indication

- I*nclude the complete reference* along with each study cited, not just the name of the senior author or name of the trial so that a reader could retrieve the source.

- I*nclude data to support claims*, e.g., absolute and relative percent reductions for the studies listed. Some studies cited present no data at all: the "NATO" study has the statement that the study ". . . demonstrated improved disease-free survival. . . ", and the male breast cancer indication simply states that ". . .Nolvadex is effective".

- Revise the description of the Royal Marsden Study for reduction in incidence in breast cancer. This study, though different in some respects from the P-1 trial, did have the power to detect a tamoxifen "preventive" effect, had one existed.

- Remove repetitive information: it makes for confusion and is difficult to decipher what is really important.

- Addition of information from other tamoxifen studies including possible adverse events not monitored in the P-1 trial, e.g., ocular toxicity and uterine pathology.[4-9] (In the P-1 trial, baseline endometrial sampling was optional for 11,000 out of the approximately 13,000 women enrolled in the trial and eye exams were not required.)

- Addition of exclusion criteria that were used in the P-1 trial *and that are not in the current label:*

  Life expectancy less than 10 years;
  Prior or suspected breast cancer of any type (invasive; DCIS; or LCIS treated with mastectomy, radiation, or systemic adjuvant therapy);
  Prior malignancy less than 10 years ago, except CIS cervix or basal/squamous cell

carcinoma of the skin;
Existing nonmalignant disease which precludes use of tamoxifen;
Performance status that restricts normal activity for a significant portion of the day;
Estrogen or progesterone replacement therapy, oral contraceptives, androgens (unless stopped three months before taking tamoxifen);
Prior use of tamoxifen;
Prior history of macular degeneration;
Concurrent use of chemotherapy;
Refusal to undergo endometrial sampling or unsuccessful sampling (if the woman has an intact uterus).

- Add a clear statement as to who should and should not take tamoxifen and why.

- Express drug levels in animal studies as multiples of the human exposure based on surface area (not milligrams/kilogram).

- Emphasize the increased incidence of serious adverse effects in women over 50.

- Add a contraindication for nursing mothers.

- Add a clarification of the Gail model software such that users realize its limitations . Research using a very large database (115,000 women followed for 12 years in the Nurses' Health Study), have found that the Gail model over predicts the risk of breast cancer.[10] The Gail model omits completely any discussion of factors that *may decrease risk* and that may be equally important in a woman's decision to use or not use tamoxifen.

  The emphasis on an absolute number (1.7% over 5 years) to determine whether to start tamoxifen is very misleading since NCI admits that "other risk factors for breast cancer have been identified or proposed. . . ",[11] although the NCI has not been able to incorporate these factors into their calculations. In the P-1 Trial, women taking tamoxifen with a five-year predicted risk of breast cancer of 2.0 to 5.0% were not statistically better off after treatment, than women receiving placebo with a similar 5 year risk, indicating a weak predictive relationship.[12]

---

[10]Spiegelman D, Colditz GA, Hunter D, Hertzmark E. Validation of the Gail et al. model for predicting individual breast cancer risk. *Journal of the National Cancer Institute* 1994;86:600-607.

[11]NCI website; http://cancernet.nci.nih.gov; "Estimating breast cancer risk"

[12]Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the national surgical adjuvant breast and bowel project P-1 study. *Journal of the*

CONCLUSIONS: The results from the P-1 trial suggest that treatment with tamoxifen causes a 49% relative reduction to placebo in invasive breast cancer. However, when one converts the data to the actual number of women affected, the picture looks somewhat different. The average annual rate of invasive breast cancer for all women in the P-1 trial was 0.68 cases/100 women on placebo and 0.34 cases/100 women on tamoxifen per year. Multiplying by 5 to get the 5-year total, one finds that 3.4 high-risk women on placebo and 1.7 on tamoxifen would be expected to get invasive breast cancer over that time period. The small difference between these numbers (coupled with the risks of treatment) is the reason for our concern about using tamoxifen to treat large numbers of healthy women for many years.

Another way of looking at risks versus benefits is to calculate the "number needed to treat" (see the October 29, 1998 Public Citizen petition to FDA). Treating 77 women with tamoxifen is expected to "prevent" one invasive breast cancer; at the same time, one in 83 (almost the same number) would be expected to get endometrial cancer.

Where risks and benefits are not clearly and fully stated and, in fact, may not be clearly known, decisions become guesswork, rather than rational choices. Given the amount of misinformation that is being disseminated to the public through many sources[13, 14] and the importance of informing patients and health professionals of both the benefits and risks, we feel that a source of clear, unbiased information is urgently needed. Given tamoxifen's known potential to cause severe adverse effects in certain individuals and its unknown long-term consequences, the FDA has the responsibility to ensure that women have access to objective information about this drug. Nothing less than the future health of many women is at stake. We look forward to your prompt response.

National Cancer Institute 1998;90:1371-1388.

[13]The Lehrer NewsHour presented a segment by their health reporter on February 18, 1999 that stated that tamoxifen *prevented* breast cancer. On-air and PBS website corrections were made March 22, 1999 in response to Public Citizen letters to Jim Lehrer.

[14] FDA issued a warning letter to Zeneca (January 22, 1999) concerning its advertising brochure to physicians for containing misleading information including repeated referral to the "Breast Cancer Prevention Trial" (which misleadingly promoted tamoxifen for "prevention"), misuse of the word "uncommon" to describe the incidence of endometrial cancer, lack of adequate information on side effects, promotion of use in an unapproved patient population (those over 60 years without a risk of 1.7), misleading efficacy data, and misleading fracture data, among other things.

CERTIFICATION

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

ENVIRONMENTAL IMPACT

Nothing requested in this petition will have an impact on the environment.

Sincerely,

Elizabeth K. Barbehenn, Ph.D.
Public Citizen's Health Research Group

Larry D. Sasich, Pharm.D., M.P.H., FASHP
Public Citizen's Health Research Group

Cindy Pearson (EB)
Cindy Pearson
Director
National Women's Health Network

Sidney M. Wolfe, M.D.
Director
Public Citizen's Health Research Group

Patient Medication Guide for NOLVADEX (tamoxifen citrate tablets) for Reduction in the Incidence of Breast Cancer

Generic Name: Tamoxifen (ta-MOX-I-fen)

Medication Guides are required by the Food and Drug Administration (FDA) for medicines that pose a serious and significant public health concern.

Read this information carefully before taking Nolvadex. It is important to read this information each time your prescription is filled or refilled because new information may have been added. This summary does not tell you everything about Nolvadex. Your health care professional is the best source of information about this medicine. You should talk to him or her before you begin taking Nolvadex and when you go for regular checkups. In addition, the professional package insert provided to your doctor and pharmacist contains more detailed information.

What is NOLVADEX?
Nolvadex is a prescription medicine approved by the FDA *for reducing the incidence* of breast cancer in women who have a high risk of this disease. *There is no evidence that Nolvadex prevents breast cancer.* Although a study has found there were fewer cases of breast cancer in women taking Nolvadex compared to women on placebo, no one knows if the drug prevented breast cancer from occurring or if the cancers were delayed and will appear later. This study was too short to assess whether longer exposure to Nolvadex would cause other types of cancer to develop or whether cancer rates might increase after women stopped taking the drug.

How does NOLVADEX work?
Nolvadex can be classified as either an anti-estrogen or an estrogen (a female hormone). Nolvadex, like estrogen, does different things in different parts of the body, which may be why it can keep some breast cancers from developing but can also cause the lining of the uterus to grow.

What clinical studies have been done with NOLVADEX?
In the United States, the only completed study assessing Nolvadex in reducing the incidence of breast cancer included 13,000 women at high risk for invasive breast cancer. This study is known as the Breast Cancer Study. Half of the women took Nolvadex (20 mg a day) and half a placebo (a sugar pill).

The women were at least 35 years old and had a combination of risks that made their chance of developing breast cancer relatively high. These risk factors included early age at first menstrual period (before age 12), late age at first pregnancy (first full-term pregnancy after age 30), fewer pregnancies, close family member with breast cancer (mother, sister, or daughter), a history of previous breast biopsies, or having high-risk changes in the breast seen on a biopsy.

The women were followed for a median time of 4.2 years. In the Nolvadex group, 2.2% developed breast cancer compared to 4.3% in the placebo group. However, the numbers of deaths from breast cancer, as well as deaths from any cause, were about the same in the two groups.

In Europe, there are two ongoing studies with Nolvadex in women with a high risk of breast cancer. These studies have shown no difference in the number of breast cancer cases between the women who took Nolvadex and those who took a placebo. These studies were smaller and the populations were somewhat different from the Breast Cancer Trial conducted in the U.S. However, the study done in England was large enough to have been able to detect the difference in breast cancers had one existed.

How do I weigh the risks and benefits of Nolvadex?
In the Breast Cancer Trial, some women experienced serious adverse effects with Nolvadex; some women also experienced complications related to the treatment of these adverse effects. These adverse effects can be fatal or disabling. The table below is intended as an aid in weighing the potential benefits (a reduction in the number of new cases of breast cancer) against the adverse events of Nolvadex.

EFFECTS OF NOLVADEX THERAPY

	Cases per year for every 1000 women taking NOLVADEX	Cases per year for every 1000 women taking PLACEBO	Difference between Nolvadex and Placebo (cases per year for every 1000 women)
BENEFIT			
Breast Cancer	**3.6**	**6.5**	**- 2.9 (*fewer cases*)**
RISKS			
Uterine Cancer	**2.3**	**0.9**	**+1.4**
Blood clot in the lungs	**0.8**	**0.3**	**+0.5**
Blood clot in the veins	**1.3**	**0.8**	**+0.5**
Stroke	**1.4**	**1.0**	**+0.4**
Sum of All Serious Adverse Events			**+2.8 (*more cases*)**

Nolvadex produced a reduction of 2.9 cases of breast cancer per 1,000 women per year (the benefit) but also increased by 2.8 the number of life-threatening adverse events such as uterine cancer, blood clots, and stroke. There was no difference in overall survival and no difference in the number of women dying of breast cancer (6 on placebo and 7 on Nolvadex). These numbers apply to the women who participated in this trial, 75% of whom had a risk of breast cancer of 2.0% or greater. Women with a lower risk would be expected to have less benefit from Nolvadex.

Nolvadex is a known cancer-causing agent that increases your chance of developing cancer of the lining of the uterus.

The likelihood of adverse reactions is much higher in women 50 years of age and older.

Cancers in rats and mice:
Nolvadex causes cancer of the liver in rats and cancer of the ovaries in mice.

Changes in human DNA:
Nolvadex has been shown to cause changes in the DNA of human cells, the first step in development of tumors.

What NOLVADEX does not do:
Nolvadex *does not prevent* breast cancer. The breast cancers that developed in women using Nolvadex were the easiest ones to treat: small tumors and those with estrogen receptors. Nolvadex treatment does not guarantee that if a breast cancer occurs it will be diagnosed at an early stage. Nolvadex does not affect survival. We do not know whether taking Nolvadex for five years only delays the appearance of cancer or actually decreases the number of tumors that will develop.

What are the most common non-life-threatening effects of NOLVADEX?
The most common non-life-threatening effects reported with Nolvadex are hot flashes, vaginal discharge or bleeding, and menstrual irregularities. These effects may be mild but can be a sign of something more serious, and women experiencing these effects should be seen by a physician. Women may also experience hair loss or skin rashes. Approximately 15% of women who took Nolvadex in the Breast Cancer Trial stopped the drug because of adverse effects.

Who should take NOLVADEX?
Your doctor has a computer program for assessing breast cancer risk. You should discuss your risks with him or her. However, this risk is only an estimate. Another study found that this computer program over estimates the risk of breast cancer. The computer program only allows the estimation of the possible benefits of Nolvadex, and does not estimate a women's risk for having serious adverse effects: blood clots, stroke, or endometrial cancer. The likelihood of these adverse effects is much higher in women over 50. You and your doctor must carefully discuss your personal medical conditions, history, and preferences to decide whether the good Nolvadex may do for you outweighs its risks.

Who should <u>not</u> take NOLVADEX?
BLOOD CLOTS: You should not take Nolvadex if you have ever had blood clots. Blood clots stop the flow of blood and can cause serious medical problems, disability, or death. Women who take Nolvadex are at increased risk for developing blood clots in the brain, lung, leg, and eye. Some women may develop more than one blood clot *even after they stop taking Nolvadex*. Women may also have complications from treating the clot, such as bleeding from thinning the

blood too much. Symptoms of a blood clot in the lungs include **sudden chest pain, shortness of breath, or coughing up blood**. Symptoms of a blood clot in the legs are **pain or swelling in the calves**. A blood clot in the legs may move to the lungs. **If you experience any of these symptoms, contact your doctor immediately.**

BLOOD THINNERS: You should not take Nolvadex if you are taking coumadin-type blood thinners.

PREGNANCY OR NURSING: *You should not take Nolvadex if you are pregnant or nursing. You should not take Nolvadex if you plan to become pregnant. You should wait for at least two months after you stop taking Nolvadex to begin a pregnancy because Nolvadex remains in the body for a long time and may harm your unborn child.* Women taking Nolvadex have had spontaneous abortions, fetal deaths, and children with birth defects; Nolvadex has the potential to cause vaginal or cervical cancer in young women exposed to the drug in the womb, a diethylstilbestrol (DES) like syndrome.

If you are capable of becoming pregnant, you should start Nolvadex during a menstrual period or have a negative pregnancy test before beginning to take Nolvadex. If you become pregnant while taking the drug, you should stop taking Nolvadex immediately and notify your doctor.

AGE: You should not take Nolvadex to decrease the chance of getting breast cancer if you are less than age 35, because Nolvadex has not been tested in younger women. You should not take Nolvadex if you are over 60 and do not have additional risk factors.

ALLERGY: You should not take Nolvadex if you have ever had an allergic reaction to Nolvadex or tamoxifen citrate (the chemical name).

EYES: Nolvadex may cause cataracts or changes to parts of the eye known as the cornea and retina. Nolvadex can increase the chance of needing cataract surgery. Nolvadex can result in difficulty in distinguishing different colors. **If you experience any changes in your vision, tell your doctor immediately.**

LIVER: An adverse effect of the liver, which may be serious, is **jaundice** (it may be seen as yellowing of the whites of the eyes).

UTERUS: Nolvadex increases the chance of changes occurring in the **lining of your uterus** (endometrium) which can be serious and can include cancer. If you have not had a hysterectomy (removal of the uterus), it is important for you to contact your doctor immediately if you experience **any unusual vaginal discharge, vaginal bleeding, or menstrual irregularities or pain or pressure in the pelvis.**

CHILDREN: Children should not take Nolvadex because the drug has not been studied in children.

Medical conditions in which tamoxifen has never been studied:

Life expectancy less than 10 years;
Prior or suspected breast cancer of any type: invasive; ductal carcinoma in situ (DCIS); or lobular carcinoma in situ (LCIS) treated with mastectomy, radiation, or systemic adjuvant therapy);
Prior malignancy less than 10 years ago (except CIS of the cervix or basal/squamous cell carcinoma of the skin);
Existing nonmalignant disease which precludes use of tamoxifen;
Performance status that restricts normal activity for a significant portion of the day;
Estrogen or progesterone replacement therapy, oral contraceptives, androgens (unless stopped 3 months before taking tamoxifen);
Prior use of tamoxifen;
Prior history of macular degeneration;
Concurrent use of chemotherapy;
Refusal to undergo endometrial sampling or unsuccessful sampling (if have intact uterus).

What should you do if you are taking Nolvadex?
While you are taking Nolvadex, you should have annual gynecological check-ups that include the uterus and breast (including mammograms). Endometrial cancer can occur in women without any symptoms, so it is important to continue with regular check-ups.

Because Nolvadex may affect how other medicines work, always tell your doctor if you are taking any other prescription or non-prescription (over-the-counter) medications, particularly if you are taking warfarin to thin your blood.

If you experience any of the following symptoms, tell your doctor immediately.
If you and your doctor decide that Nolvadex therapy is right for you, you should look for symptoms indicating that you might be experiencing one of Nolvadex's known risks.

- new breast lumps
- vaginal bleeding
- changes in the menstrual cycle
- pelvic pain or pressure
- swelling or tenderness in the calf
- unexplained breathlessness (shortness of breath)
- sudden chest pain
- coughing up blood
- changes in vision
- yellowing of the whites of eyes

If you see a health care professional who is new to you (e.g., an emergency room doctor), tell him or her that you take Nolvadex.

Who is at risk of adverse effects?
There is no way that anyone can predict whether a person taking Nolvadex will get breast or endometrial cancer, blood clots, or cataracts (unless they have had these before). The Breast Cancer Trial was too short to determine whether longer exposure to Nolvadex would cause other types of cancers to develop or whether breast or other cancer rates might increase after women stopped taking the drug.

In a trial in women being treated for breast cancer taking Nolvadex 40 milligrams per day for 4.5 years, there was a 6-fold increase in endometrial cancer several years after stopping drug treatment as well as a 3-fold increase in cancers related to the gastrointestinal tract (esophagus, stomach, colon-rectum, liver, and pancreas). In another trial in women being treated for breast cancer with Nolvadex conducted by the National Cancer Institute, *10 years of treatment resulted in worse outcomes* than 5 years of treatment.

Other sources of information:
This summary does not include all possible adverse effects with Nolvadex. If you want more information ask your doctor or pharmacist for the professional product labeling for Nolvadex.

How should I take NOLVADEX?
The dose studied in the Breast Cancer Trial was 20 mg a day for five years. Take your medicine each day. You may find it easier to remember to take your medicine if you take it at the same time each day. If you forget a dose, take it the same time the next day. Swallow the tablets whole with a glass of water. You can take Nolvadex with or without food.

How should I store NOLVADEX?
Nolvadex (tamoxifen citrate) is available as 10 mg tablets and 20 mg tablets. Store at room temperature (68-77^0 F). Keep in a dark, closed container. Keep out of the reach of children. Discard tablets after the expiration date on the container and be sure any discarded tablets are out of the reach of children.

Do not give your medicine to anyone else, even if they have a similar condition, because it may harm them.